ISSN 2278–540X EISSN 2278–5396

DRUG DISCOVERY

Drug Design: Signature of Drug Discovery

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Article History
Received: 20 November 2019
Accepted: 03 December 2019
Published: January 2020

Citation
Seenivasagam R. Drug Design: Signature of Drug Discovery. *Drug Discovery*, 2020, 14(33), 1-8

ABSTRACT

Drug is the primary key and drug discovery is the program of pharmaceutical-art for disease management. The scenario of designing potential-drugs based on identification of therapeutic targets through pathogenesis and screening of active principles by lead identification and optimization. Final stage of existing drug discovery processes brings only less than 1% of drug candidate to market research and its results shown the economic impact of drug discovery program. Hence drug designing is the most vital curriculum to save the expenditure of drug discovery and development process. The extensive perceptions of drug design in addition to the knowledge and skills in attendance have structured by the role of countless experts. Still, some fascinating confronts yet to be enlightened. Here, I summarize the significance and need of drug design.

Keywords: Drug; Drug discovery; Drug design; Drug development.

Abbreviations: CDD - Computerized drug design; FDA - Food and drug administration; PrPSc - Prion protein; nvCJD - New variant Creutzfeldt-Jakob disease or mad cow disease; PrPC - Cellular prion protein; QSAR - Quantitative structure–activity relationship; CADD - Computer- aided drug design.

1. INTRODUCTION

From genomic analysis to FDA (Food and drug administration) approval to market launch of the drug discovery cycle (Fig.1) is consumes 12-15 years and US$ 800 million for a single molecule to reach the market (DiMasi et al., 2003). Plenteous novel technologies have been explored to limit the phases of drug R&D and to reduce the outlays. The computerized drug design (CDD) is the prime technology among them (Jorgensen, 2004). Drug designing is the initial practice for building a novel molecule through computer aided molecular-modeling process by the scenarios of ligand-based and structure-based drug design. Drug design as a lead-harvesting tactic should be structured more principally and precisely, for a broader range of therapeutic competence, to mine novel healing efficacies and physiological response. Transversely, every phase of drug discovery pipeline from target identification topre-clinical analysis is the series applications which is illustrated in Fig.2 have contributes considerably within drug design (Yun Tang et al., 2006).

2. SIGNIFICANCE OF DRUG DISCOVERY: DRUG DESIGN

At this point, subsequently, we have structured some drug-discovery issues which are much responsible to prove the essentiality of drug design methodologies to generate efficacious molecules;

First - about 35, 000 genes of human-genome consists only < 10% (~ 3,000 - 3,500) of the genes are representing as superior candidates for interaction of small-molecules either as a therapeutically significant target in concerning function is still under exploration. Consequently, >28.57% (~ 10,000) of the genes are also been competent in drug response and are not annotated and the functional determination is required for that to design the novel molecules (Mario et al., 2003).

Second - conversely, the human genome possess simply ~30,000 genes, instead of100,000 which was anticipated and it's not a bit of the mater for drug discovery when compare with the combined quantity of larger proteome and immunome which is encompasses several hundred thousand of targets for direct interaction with the drugs. Consequently, the network of druggable-proteome or druggable-targetome is the huge source for future-target based drug design (Hugo Kubinyi, 2003).

Third - Single compound- single target criteria is not fit for some disease scenarios while adopt certain receptor amalgamations as targets in the form of druggable-physiome to designing of enormous novel molecules, for instance; (a) the constitutively acting BCR-ABL kinase is accessible in chronic myelogenous leukemia patients alone which is effectively inhibits by Imatinib (Gleevec;Novartis), (b) the remote binding-site or quite indirect mode are the targeting manners of majority of our drugs. The interferential activity of familiar statins in the biosynthesis of cholesterol, sexual hormones, farnesyl residues, corticosteroids and cholic acids are surprisingly not generate severe side-effects, (c) Olanzapine is a booming neuroleptic drug which is in top-20 market ranking of the world. It is acts as a nano-molar antagonist and extremely unspecific as a minimum of ten diverse neurotransmitter receptors, (d) previously, some active compounds are criticized as dirty-drugs, but now we have concluded that in certain cases a fair action at numerous targets which shows efficient therapy than high specificity, (e) the early beta-blockers are again commenced for therapy which are unspecific antagonists of β1 and β2 while the later-stage β1-specific antagonists, over and above partial agonists, including and excluding of α1-antagonistic activity (Hugo Kubinyi, 2003).

Fourth - A double tyrosine (residues 149 and 150) motif in buried helix 1 of the aberrant prion protein (PrPSc) is the binding site of quinacrine (quantity of mill molar*K*ds) to provisionally inhibits the signs of new variant Creutzfeldt-Jakob disease (nvCJD) or mad cow disease. In this case, helix 1 is transformed to β-sheet from α-helical structure during the change to PrPSc disease form from cellular prion protein (PrPC) and that inhibiting this conversion might be significant to slowing the disease which was investigated by researchers of University of Bayreuth. They suggested that, the breathing like movement (exposes helix 1 and β-sheet 2 of sub-domain) of prion protein is permitting the assessment of drug. In second case, the drug compound binds to residues of double-tyrosine in the C-terminal region of the full-length protein of PrPSc which was found by scientists of Institute for Molecular Biology and Biophysics in Zurich, Switzerland. In this case, utilization of peptides as a model structure for proteins is risk constantly. Moreover, only the mill molar concentration of quinacrine has shown the binding activity with residues of double-tyrosine. The researchers concluded that the drug is vastly concentrated in membrane compartments such as lysosomes, where PrPSc also inclines to consolidate. In both the cases, the significance of drug target is still unclear. Hence, both the teams concluded that, the structure based drug design shall assist to enhance the efficacy of drugs 10-20 fold with the bis-componds without prediction of structure (Tuma, 2003).

Fifth - structure-based and computer-aided in-silico techniques are decision-making and also non-expensive tools in drug-discovery, when contrast with the cost-effective approaches of classical medicinal-chemistry is a rising propensity to mishandling of such terms and to overestimate their significance, and to over-emphasize ADME issues in clinical-failure (Hugo Kubinyi, 2003). Nearly 70% of the expenditure out of US$ 800 is related with molecule failures in drug development process. Subsequently, the number of New Molecule Entities approval rate also been declined in recent years (Fig.3).

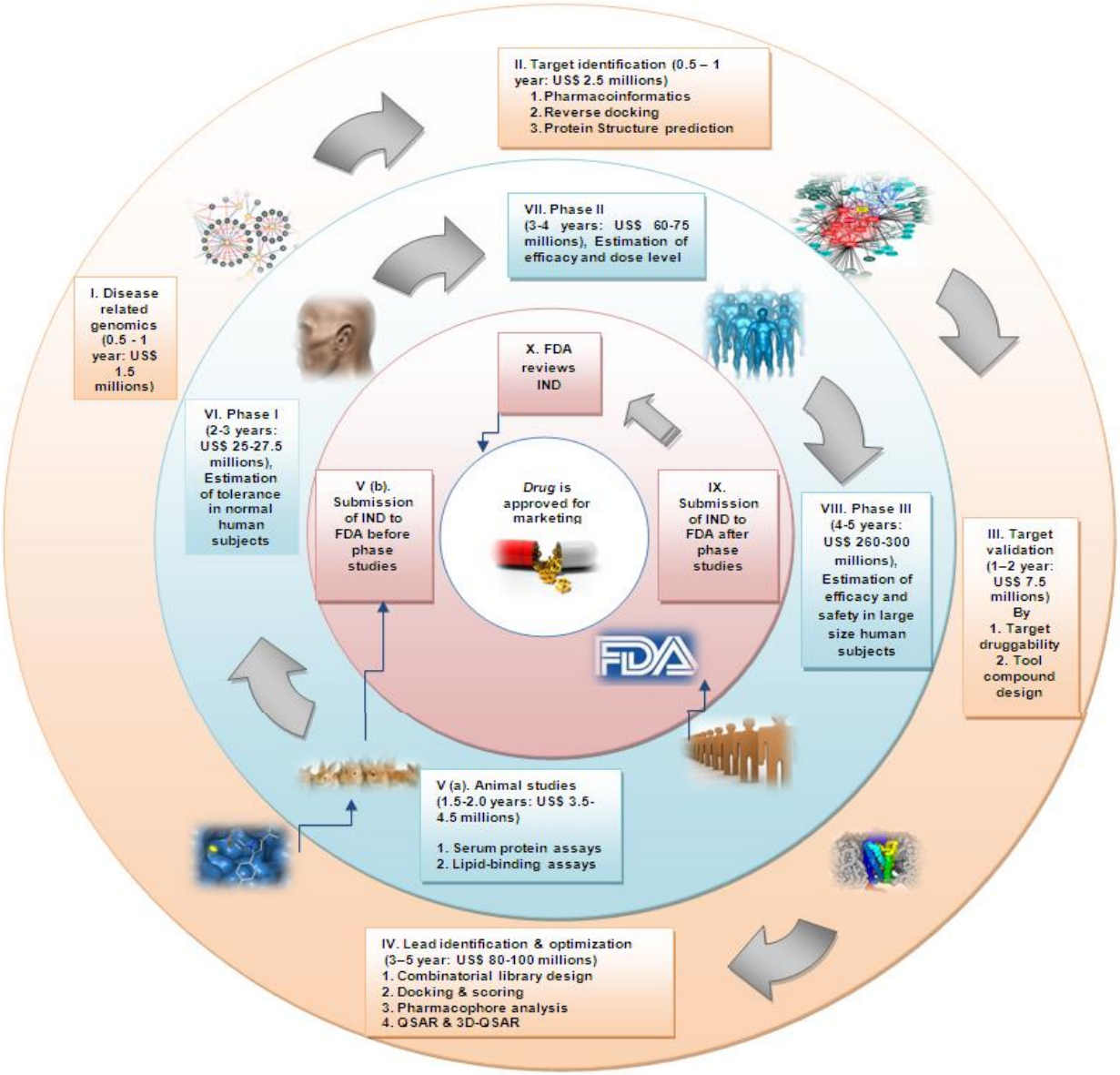

Figure 1

Phases of drug discovery and development is illustrated by Onion model. Developing drugs is a very complex process and very expensive. When the total cost of almost a billion dollars over 10-15 years (Dickson & Gagnon, 2004; Paul et al., 2010) the cost of the final stages of friction are important to reduce as much as possible (Rawlins, 2004). The process of drug discovery begins with the identification of a medical need, including a decision on the adequacy of existing treatments. This analysis and assessment of current knowledge of the target disease, the hypotheses on how to potentially improve the treatment - ie, efficiency, safety and mechanical improvements in the method in advance novel drug therapy in patients with the disease target? Based on these assumptions, the specific objectives set for the project. Then, the forecast pharmacoinformatic and physiologically pharmacokinetic simulations (IV-lead identification and optimization) can be implemented to model the pre-clinical, which is usually built into the stage of discovery in-silico lead to lower cost (Tang et al., 2006). Key next steps include detecting relevant biological activity (a "hit") for a structurally novel compound in vitro, then finding an agent linked to the activity in vivo in an appropriate animal model, followed by maximizing this activity in the preparation of similar structures, and finally choosing a drug as the drug candidate. This drug candidate was done for the toxicological tests on animals, as the law requires (Cooper, 2002). If the substance passes all these tests, all the accumulated research data collected and presented as a New Drug Application (IND) to the Food and Drug Administration (FDA) United States (or equivalent in other countries) before clinical trials began. In the clinical evaluation is under assessment in healthy volunteers of toleration (Phase I), efficacy and dosing in patients (phase II), followed by extensive studies of thousands of patients appropriate to develop a wide database of safety and efficacy. In clinical trials, the patient sample is chosen by the mode of biomarker (genotypic or phenotypic), (Eichler et al., 2011). Drug candidates for rare (4-7%) that survive this series of tests of development, a New Drug Application (NDA) containing all the accumulated research data will be archived for further consideration by experts of the FDA. Only the approval of new drugs can be offered to physicians and patients in the treatment of disease, in which it was, designed (Lombardino et al., 2004).

Figure 2

The sequence of drug design in drug discovery pipeline. The drug design series possess four significant roles and also subdivided to various tools, they are;from Target identification (Bioinformatics, Chemo-informatics, Pharmaco-informatics, Immuno-informatics, and Pharmacogenomics) to Target validation (Target druggability, Tool compound design, Pseudo receptors, Target specificity and Virtual target models), and from Lead discovery (Pharmacophore modeling, Combinatorial library design, De-*novo* based design, Fragment-based design, and Docking & scoring) to Lead optimization (QSAR, 3D-QSAR, Structure-based optimization, biological-activity based optimization and Chemical-synthesis based optimization) to Pre-clinical *insilico*analysis (*Insilico* ADME-prediction, *Insilico* immunogenicity, *Insilico*toxicity, ADME simulations and prediction of biological activity).

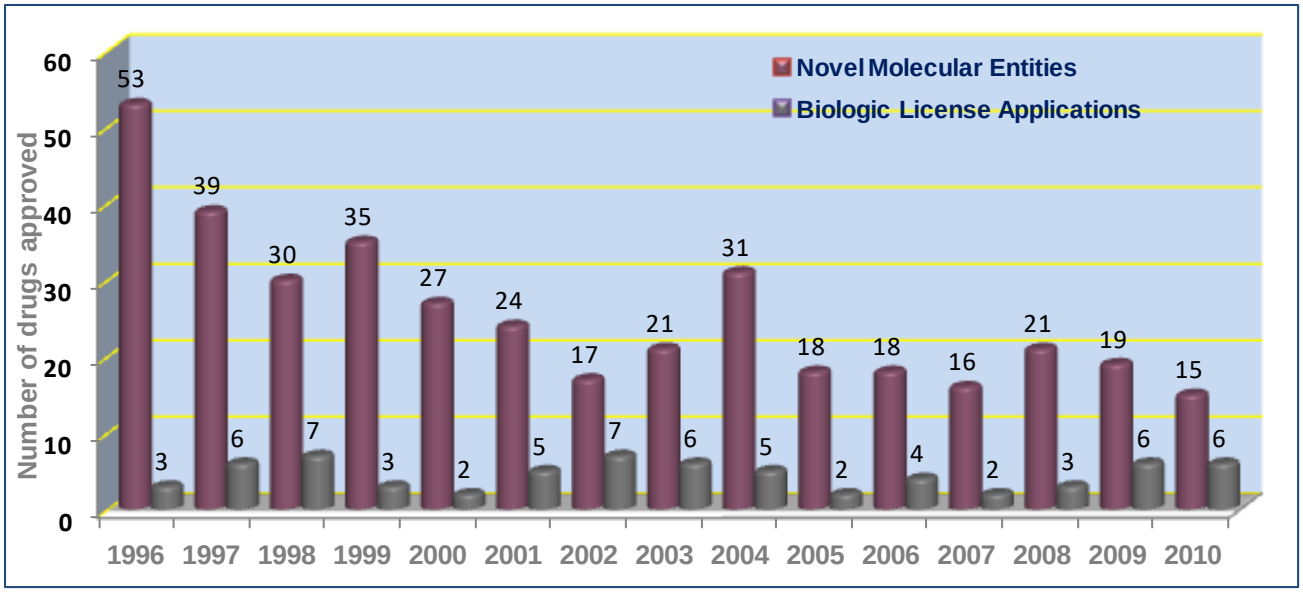

Figure 3

New molecular entities and biologic license applications permitted through the US FDA's Center for Drug Evaluation and Research by annually. US-FDA approved 16 new molecular entities (NMEs) and 2 biological license applications (BLAs) in 2007, and 15 NMEs in 2010 were the lowest number recorded since 1983. The US-FDA approvals in 2008 amounted to 21 NMEs and 3 BLAs have been evaluated by the Center for Drug Evaluation and Research (CDER). For some, this small increase in approvals compared to previous years due to the optimism. 19 NMEs and 6 BLAs approved in 2009, by the CDER in US-FDA- Just one more than in 2008. In 2010, the US FDA's CDER approved 15 NMEs and 6 BLAs (Hughes, 2008, 2009 & 2010; Mullard, 2011).

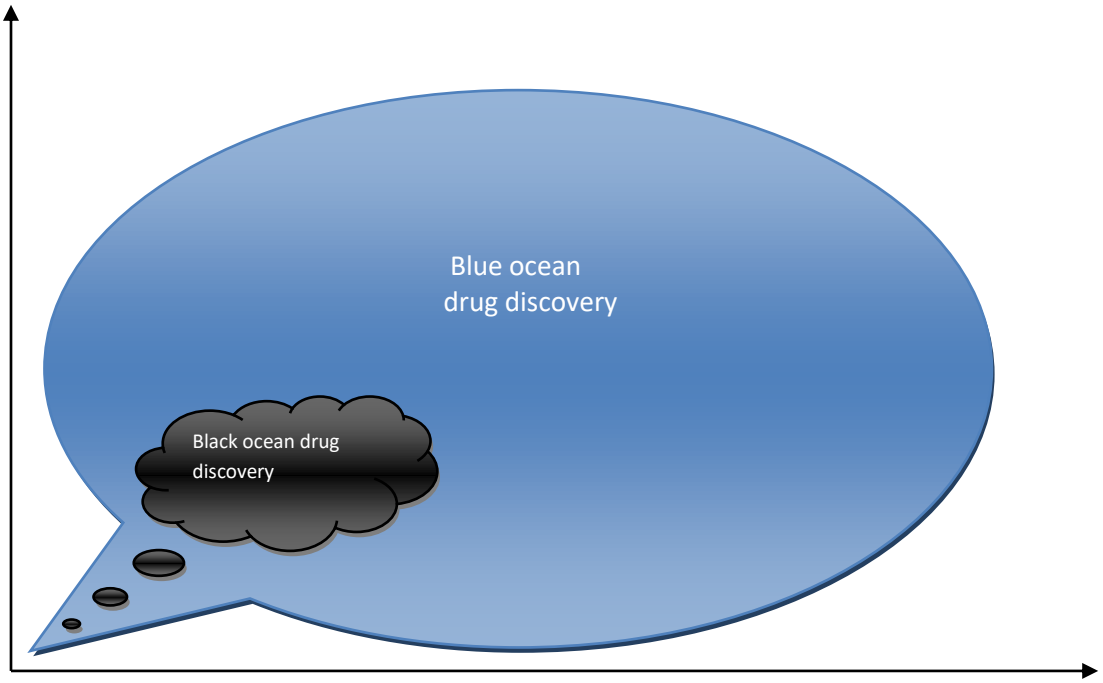

Figure 4

In the illustration of blue ocean strategy, the cost-effectiveness, clinical failure and withdrawn drug from marketing due to adverse reactions are denoted by black ocean drug discovery. The significant drug design process shall offer more efficacious molecules with minimized research cost and without adverse reactions to the market which is represented by blue ocean drug discovery. The X-axis indicates failure of molecule, cost-effectiveness and reward, whereas the Y-axis indicates novelty (Kim and Mauborgne, 2005; Youssef L. Bennani, 2011).

Table 1 Drugs withdrawn due to safety issues identified after marketing (Julio Licinio and Ma-li Wong, 2002)

Drug	Approval date	Date withdrawn	Indication	Sales at withdrawal
Duract	Jul-1997	Jun-1998	Short-term pain management	$50 million
Pondimin	-	Sep-1997	Obesity	$106 million
Posicar	Jun-1997	Jun-1998	Hypertension and chronic angina pectoris	$41 million
Propulsid	Jun-1993	March-2000	Gastro-esophageal reflux disease	$975 million
Raxar	Nov-1997	Oct-1999	Community-acquired infections	$17 million
Redux	Apr-1996	Sep-1997	Obesity management	$114 million
Rezulin	Jan-1997	Mar-2000	Type-2-diabetes	$600 million
Rotoshield	Aug-1998	Oct-1999	Rotavirus vaccine	$43 million
Seldane	May-1985	Dec-1997	Seasonal allergic rhinitis	$90 million
Trovan	Dec-1997	Jun-1999	Infections	$160 million

DiMasi et al. (1991) have recommended that the 20-23% of outlay would be reduced, due to the reduction of 1-2 years in the drug development period, and that a 2% raise of drugs achieving the clinical analysis from phase I studies would decline the expenditures by ~10% (DiMasi et al., 1995). A US survey in the year of 2000 regarding the prescription of drugs which was produced US$ 1.3 million per day as the revenue, and in the survey of Prilosec® (an anti-ulcer drug) this digits leapt equal to US$ 11.2 million per day (Getz et al., 2000). These rewards shall make a massive drive in the core of the pharmaceutical firm to design and discover novel drug-targets and to better identification of efficacy of compounds presently on the market place. This is desolately borne-out through the reality that in the recent-years, at any-rate 10 compounds that have been effectively endorsed for the treatment were withdrawn by reason of adverse effects recognized and acknowledged later (Table 1). In this case, cost effective scenario of drug discovery can be correlated in presence and absence drug design (Fig.4) by the universal marketing based strategy of Blue-Ocean (Kim and Mauborgne, 2005; Youssef L. Bennani, 2011). Black oceans are all the drugs in market today – the known drug discovery space without drug design techniques. In the black oceans, drug discovery limits are defined and acknowledged, and the cost effectiveness, efficacy and adverse reaction of molecules are known. Here research laboratories try to surpass their competitors to snatch a larger share of innovation through drug discovery without drug design. As the drug discovery space gets crowded, prospects for proceeds and development are reduced. Blue oceans, in contrast, denote all the drugs not in market today- the unknown drug discovery space with drug design techniques. In blue oceans, stipulate is fashioned rather than fought over. There is plenty of opportunity for drug-discovery that is both speedy and beneficial. In blue oceans, the drug-discovery contest with drug design is irrelevant because the rules of the research are waiting to be set. Blue Ocean is an analogy to depict the wider, deeper prospective of drug-discovery space with the influence of drug design strategies, that is not yet explored. Hence drug design is an unavoidable and most efficient tool for decision-making on molecules in early stage of every drug discovery route.

The drug-discovery period from 1960 to 2000 has shown unprecedented development in drug design as of the concept of quantitative structure–activity relationship (QSAR) analysis to structural biology and computer- aided drug design (CADD). CADD has been utilized in designing decidedly selective drug-candidate against certain receptors (for instance: p90 ribosomal protein S6 kinase) which is tricky to be done by other techniques (Cohen et al., 2005). Ligand discovery and optimization are functioned as conventional applications of drug-design while screening of target, validation and prediction of ADMET are modern perceptions.

3. CONCLUSION

Drug design have a significant influence on drug discovery through Pharmacogenomics, Pharmacoinformatics and the methodological supports of structure-based, ligand-based and computer based approaches. Small SNP-induced amino acid modifications can cause subtle changes in bio-molecular structure will intensely affect the search for personalized therapies. Near feature, superior prominence will be positioned on very specific diversity in drug structures that select among mutated proteins. In addition to being biologically challenging, present approach will evidently encompasses significant fiscal effects on the pharmaceutical firms. The active excretion of drug molecules from cells, as with multiple drug-resistances that arises in cancer chemotherapy may include in mechanism of elimination. The patients who are all identified with genotypes for particular MDR-pathways could be treated with alternative methods. The population variations in drug metabolizing enzymes are habitually associated with pharmacogenetic differences in the response to drugs. Before the commencement of compound synthesis, the homology models or crystal structures of these enzymes can be utilized for screening of compound and designed through de*novo*

methods. This can be preceded at two phases as follows; (a) to identify the principal pathway of expected metabolism, the metabolism prediction programs such as Meteor (Greene et al., 1999) or Metabolexpert (Darvas, 1988) can utilize virtual compounds as input, (b) the structural models of the metabolizing enzymes which including the known SNP variants can be exercised to screen virtual compounds. The cytochrome P450 isozymes which are participated in oxidative drug metabolism broadly assumed to these procedures. The efficacy of clinical trials by focusing concentration on the response of particular subpopulations to drug treatment will be enhanced by genomic pre-screening of patients for SNP population in drug metabolism. The consequences of drug design approach are that it should be promising to industrialize the establishment of individual therapies.

SUMMARY OF EDITORIAL

1. Designing potential-drugs based on identification of therapeutic targets through pathogenesis and screening of active principles by lead identification and optimization.
2. Drug design is an unavoidable and most efficient tool for decision-making on molecules in early stage of every drug discovery route.
3. Drug design have a significant influence on drug discovery through Pharmacogenomics, Pharmacoinformatics and the methodological supports of structure-based, ligand-based and computer based approaches..

FUTURE ISSUSES

New developments in the sequence of genomics to clinical studies will impact on drug design at three major heights as, 1) the drug-receptor interaction at the binding site, 2) drug absorption and distribution, 3) the elimination activity of drugs from the body. For the development of personalized medicines, the above key-points shall have to be tackled. The drug design technologies and its policies with SNPs (in terms of mutated binding-sites)and the out-coming modifications that occur in response to therapeutic-medicines. In these cases, drug-design strategies may require to be customized for novel-construct of drug molecules that would be choosy and efficient in the mutated site. Based on the polar surface area of molecule which is governing solubility and computations of logP (the octanol/water partition coefficient) are responsible for absorption in terms of physic-chemical transport process. It is feasible that, the pharmacokinetic properties of compounds will affect by SNPs in drug transporter genes and, hence these may enclose to take into concerning for the drug design process.

Funding:
This study has not received any external funding.

Conflict of Interest:
The authors declare that there are no conflicts of interests.

Data and materials availability:
All data associated with this study are present in the paper.

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